GENETICALLY DETERMINED TUMOURS IN DROSOPHILA MELANOGASTER

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The research of tumours became an important problem of biology and medicine in the last few decades. This problem has been intensively investigated in vertebrates (in invertebrates the situation is different in spite of the fact that also in them noticeable abnormal tissues and cell groups are to be found).

Works on abnormal tissue growths in insects apply a most diversified nomenclature which indicates that the two kinds of abnormality are non – homologous at least in case we consider the characteristics of malignant tumours in vertebrates (i. e. uncoordinated growth, autonomous metabolism, invasive character, changed cell surface). In this sense, according to Harshbarger and Taylor (1968) no malignant tumour exists in insects, although other investigators deny this (Gateff et al 1968).

The ontogenesis of insects has special properties characteristic only of them, for instance, except some cell types there is no cell division in adults which results in a disability of the malignant cells to multiply. This is one of the reasons why tumours lack or infrequently occur in adults. The latter fact seems to be supported by King (1969) who discovered uncontrolled cell division with the reproductive organ multiplying in imaginal age, which resulted in the development of an ovarian tumour in *Drosophila melanogaster*.

Metamorphosis also puts a stop to tumour development in adults. Imaginal discs and histoblasts in larval age are not functional parts of the larvae and – when formed – larval tumours disappear at metamorphosis.

On the other hand the absence of dispersion of abnormal tissues may be explained among others by the difference between the circulation of insects and vertebrates as well.

Further on the genetically determined abnormal tissues as described in *Drosophila melanogaster* will be dealt with.

The genetic factors taking part in tumour development are at least partly known. In *Drosophila melanogaster* the abnormal growths are of most diverse appearance and also show differences as to their effects.

Tumorous head (tu – h)

The investigations concerning with the tumorous-head (tu – h) strain of Drosophila connect with the name of G a r d n e r (1970).

Tumorous head malformations are different in size; they are benign. They may appear round the eye and antenna in the form of small protuberances but they may also grow to an amorphous tissue mass occupying a considerable part of the head (Gardner 1970.). Histologically the tumours are built up of abnormal epidermal cells. Mesenchyma cells and/or muscle cells may be present inside the tumours.

The mutant larvae have a prolonged larval stage. Larvae incapable of pupation were described by K o b e l and B r e u g e l (1967) as lethal tumorous larvae (ltl). Both the extension of the larval stage, and the absence of pupation are associated with an abnormal hormonal milieu (defect of the juvenile hormone metabolism).

According to genetic studies the formation of tumorous head character is controlled by two genes, namely tu – 1 and tu – 3. The recessive tu – 1 is located in the sex chromosome (X), and it has no independent phenotypic influence on the tumorous head trait; tu – 1 is a specific modifier of tu – 3. The position of the tu – 3 gene is located at the 58 th map unit of the third chromosome. It is a semidominant gene. The phenotype is influenced by a polygenic system of modifier genes.

Lethal giant larva ($1/2/gl^4$).

Earlier G a t e f f et al. (1969) examined the $1/2/gl^4$ *Drosophila* mutant. This mutation is a recessive one located at the 2^{nd} map unit of the second chromosome. The homozygous mutant larvae have an invasive neuroblastoma of the larval "brain". According to the authors it is a malignant, transplantable and lethal tumour, consequently a real neoplasm in vertebrate sense. The cells of the nerve system lose their organ-specific character, the "brain" of the larvae grows and the larval structure disintegrates without a differentation of the imaginal structure having been started, and as a result, the larva dies (Fig. 1.).

The examination of the central nervous complex of the mutant showed that the lobes of the mutant "brain" became progressively deformed, the different cell types were not localized to specific areas as in the wild-type brain (this complex consists of two brain lobes and a ventral ganglion). (Fig. 2 ,3).

Fragments of the third instar mutant brain behave differently than the wild brain fragments following the implantation as well. The mu-

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tant brain fragments grew rapidly after the implantation into a female abdomen and invaded the ovarium, midgut, killing the host within 6 days. In vivo the fragments of wild-type continued their growth in the adult host, until finally reaching the size of a fully grown third instar larval brain whose structure was compact and never killed the

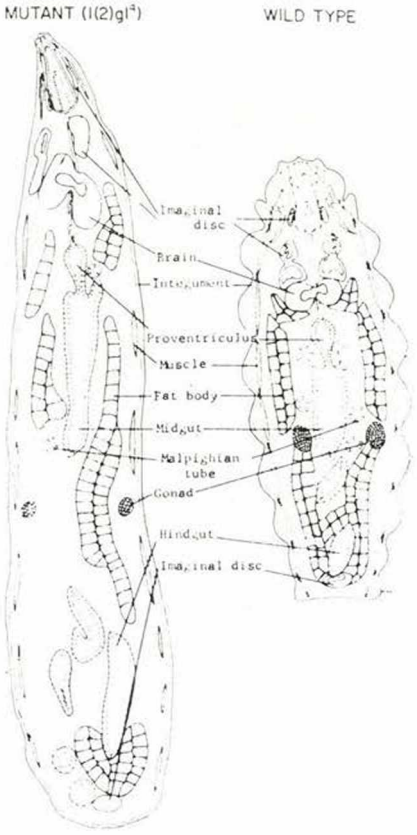

Fig. 1. Third instar mutant (1/2/gl⁴) and wild-type larvae (From G a t e f f and S c h n e i d e r m a n 1969)

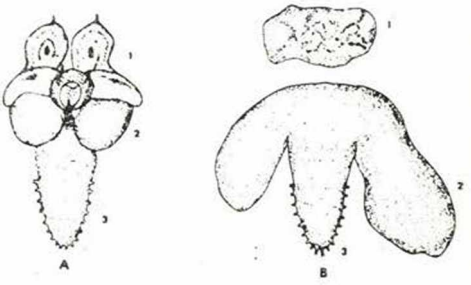

Fig. 2. Cephalic complex of: A third instar wild-type larva, B mutant larva. 1: eye-antennal disc; 2: brain; 3: ventral ganglion. (From G a t e f f and S c h n e i d e r m a n 1969.)

host. Similar differences can be seen at the in vivo cultivation of the wild and mutant imaginal disc, too: the fragments of wild-type imaginal discs usually metamorphose with the host larvae and then produce a specific integumentary structure (autotypic tissue – H a d o r n 1966). Similarly to the atelotypic tissues (H a d o r n 1966) the mutant disc cells kill the host and never form specific stuctures.

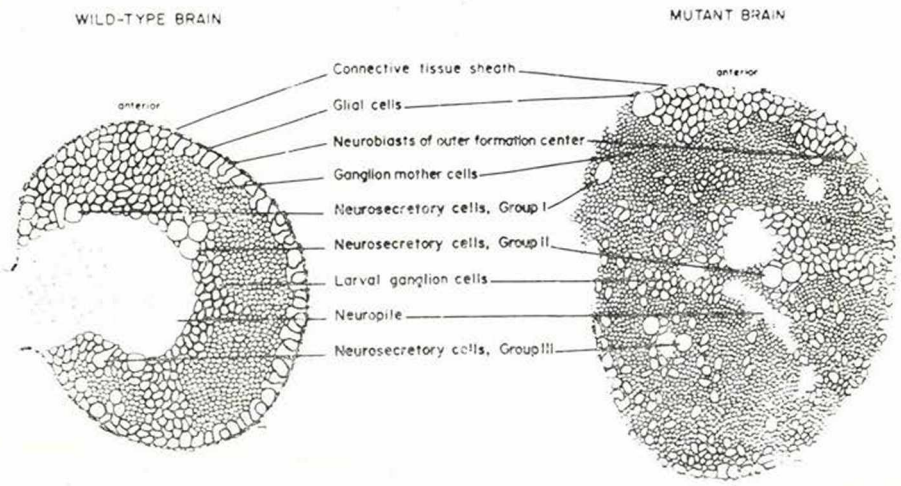

Fig. 3. Frontal section through third instar wild-type and mutant ($1/2/gl^4$) brain (schematic). (From Gateff and Schneiderman 1969.)

Ovarian tumours

King (1969) studied the ovarian tumour mutant of *Drosophila*. In the ovary of the animal of tumorous genotype the inhibition of cell division stopped, which resulted in hundreds or thousands of cells in the egg chambers. These flies were sterile. The frequency of occurrence of tumors increased with the age of animals.

In the production of a similar phenotypic effect two genes are involved:

a) *fused (fu) gene*

This gene is localized at 59,5 on the linkage map of the X chromosome and has a recessive pleiotropic effect (it influences the wing veins and embryogenesis). The *fu* tumours appear gradually in adult. The *fu* gene has some alleles which differ from each other in the rate of ovarian tumor formation ($fu^{59} < fu^{1}$; fu^{62}). Where the fusion of a normal and a tumorous chamber takes place, the tumor cells infiltrate into the normal chamber, in this sense *fu* tumor cells are invasive.

b) *female sterile (fes) gene*

The recessive gene *fes* was localized at 5 on the linkage map of the 2*nd* chromosome. The homozygous male is fertile while the female is sterile. The *fes* gene causes abnormality only in the ovarian and acts earlier in ontogenesis than the *fu* gene. The examination of animals of

fu/*fu*; *fes*/*fes* genotype showed that the *fes* was epistatic to *fu*. King (1969) supposes a dimeric mitogen agent which can shorten the interphase resulting in acceleration of cell division and by this reduction in cell volume is brought about during the succesive divisions. According to the hypothesis division is inhibited when the cell volume falls to the critical minimum value (50 μ^3). The ovarian tumorous mutants produce instable mitogen which results in the prolongation of the intermitotic period and thus the cells never reach the critical minimum volume required for stopping further divisions.

Melanotic tumours

Melanotic tumours were found in 55 strains of *Drosophila*. They are also called melanotic pseudotumours, melanomas.

Depending on the strain, the shape, size, number, location and appearance of the tumours are variable. They may appear as single cell masses or complex bodies free-floating in the hemolymph. In most cases they are connected with the hemolymph cells. In the tumorous strains the plasmatocytes may release from the lymph gland and transform into lamellocytes during early larval life; this tranformation normally occurs at the time of pupation. From this early transformation the conclusion is drawn that the metamorphosis of the hemocytes may be pathological. The next step is the aggregation of the hemolymph cells, and this becomes complete at the end of the larval period. The aggregates may consist of several cell types. The lamellocytes are at the surface of the tumour while inside it there are round or polygonal cells to be found (R o t t i n o and K o p a c 1966, Ghelelovitch 1969.).

At the later stage of tumour development the cells become pigmented with melanin; the appearance of pigmentation coincides with the degeneration of the cells. Some authors (R i z k i 1957, R o t t i n o and K o p a c 1966) consider the melanotic tumours a manifestation of inflammatory or degenerative processes because mitotic formations are not to be found in them and sooner or later the cells lose their ability to function.

Others (G h e l e l o v i t c h 1959, H a r n l y 1963) beleive that a neoplastic process may contribute in melanotic tumour formation. The polygonal neoplastic cells are components of the tumours (these cells derived from the large hemocytes to be found in the tumorous strains). The multiplication of the polygonal cells may be stopped by their encapsulation with the spindle-shaped cells (this process can be generally seen in insects at infection). Thus, two different events should form a melanotic tumour: one of them is a neoplastic process, the other an inflammatory one which is a subsequent reaction to the first process. The results of these events are the degeneration and melanization of the tumour cells.

The tumour genes (tu-genes), primarily responsible for tumour formation are located mainly on the second chromosome and are recessive (Barigozzi 1969), still the manifestation of the melanotic tumorous character is controlled by the complex genotype (polygene system). The tu-genes are not allelic in the different tumorous strains, and the different genes determine different incidences and sites of tumours.

Also such melanotic mutants are known in which the tumorous character is controlled by a single factor (Barigozzi and Sari Gorla 1968).

Summary

The origin and nature of the tumorous changes in insects are not clear yet, but it is a fact that they do not correspond to vertebrate tumours wich means that the term "tumour" covers different alterations in insects and vertebrates. All this does not mean that insects are incapable of developing true neoplasms or that insect neoplasms should necessarily present characteristics of vertebrate neoplasms. A continuously growing number of researchers accept the assumption that formation and growth of abnormal cell groups described as tumours in insects result from abnormal cell accumulation, however, not from irregular cell division.

The genetic determinants of certain types of tumours in *Drosophila* are well known, in case of others, for example in melanotic alterations the whole genom takes part in tumour formation. The fact that in case of melanotic tumours numerous non-allelic genes develop similar phenotypes makes the elucidation of the role of the genetical factors more difficult. A further problem in the examination of insect tumours: the penetrance of tumour-forming genes is greatly influenced by the environmental factors. Progress in studies of insect oncology will probably lead to a situation where the subject of the investigations will not be to search for homology with the vertebrate neoplasms but a more perfect knowledge of the characteristics and inducing factors of insect tumours.

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